



Literature Review of Air Pollution-
Related Health Endpoints and
Concentration-Response Functions
for Particulate Matter:
Results and Recommendations

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INTRODUCTION

Every four years, the South Coast Air Quality Management Board (SCAQMD) updates the regional Air Quality Management Plan (AQMP) for Los Angeles, Orange, Riverside, and San Bernardino Counties in southern California. As part of the development of this Plan, SCAQMD considers the socioeconomic impacts of the AQMP. These estimated benefits and costs are detailed in a Socioeconomic Report that accompanies the AQMP.

A key analysis in the Socioeconomic Report is an assessment of the health benefits of the AQMP on residents of these four counties. This assessment of health impacts relies on data describing the baseline incidence of mortality and morbidity endpoints, the estimated change in air pollution concentrations, and the relationship between exposure and health outcomes. SCAQMD draws this latter input from population-based epidemiological studies. These studies provide information on which health endpoints are associated with exposure to air pollutants, and the mathematical relationship between exposure and the outcome. This report presents our review of recent studies of the health impacts associated with exposure to particulate matter (PM) and provides recommendations to inform SCAQMD's decisions regarding which health endpoints to include in its benefits analysis of the 2016 AQMP and which mathematical functions should be used to evaluate each endpoint.

METHODS

Our approach consisted of three steps. First, we identified the endpoints and studies used in SCAQMD's 2012 Socioeconomic Analysis. Second, we reviewed the current evaluation of PM effects by the U.S. Environmental Protection Agency (EPA) in its most recent Integrated Science Assessment (ISA) document (U.S. EPA, 2009). Finally, we conducted a supplemental review of the health literature published since SCAQMD's 2012 Socioeconomic Report.

2012 SOCIOECONOMIC REPORT

IEc sought to identify the health endpoint categories and health studies used to evaluate the health benefits of the 2012 AQMP. IEc based its findings of the 2012 categories and inputs based on review of the 2012 Socioeconomic Report and appendices, additional background documentation provided by SCAQMD, and our knowledge of the standard BenMAP functions typically used at the time of the last assessment.

EPA INTEGRATED SCIENCE ASSESSMENT

In addition to our literature review, we also reviewed the most recent Integrated Science Assessment for PM published by the EPA in 2009. The comprehensive assessment of the health literature presented in the ISA provides EPA's current assessment of the strength of the evidence linking PM exposures with an array of health endpoint categories and thus serves as a suitable baseline against which we can compare the findings of recent research.

SUPPLEMENTAL LITERATURE REVIEW

In order to ensure SCAQMD uses the most current science when evaluating the health impacts of air pollution control, we conducted a literature review on mortality and morbidity impacts of PM, both particles less than 2.5 microns in diameter (PM_{2.5}). (Similar searches were also conducted for ozone (O₃), nitrogen oxides (NO_x), and sulfur dioxide (SO₂); results for these pollutants will be reported in a separate document.). We searched PubMed and Google Scholar for peer-reviewed articles on PM from 2012 onward, using search terms "PM_{2.5} AND mortality" and "PM_{2.5} AND morbidity." We also included several studies that did not appear in our search but were recommended by our scientific advisor, Dr. George Thurston. We prioritized studies to evaluate for inclusion in the Socioeconomic Assessment by evaluating them using the criteria described in our Evaluation Criteria Memo to SCAQMD dated August 20, 2015; these criteria are summarized in Exhibit 1. Our criteria serve as guidance for evaluating studies and weighing their strengths and limitations. No one study is likely to meet all criteria listed.

EXHIBIT 1. CRITERIA FOR EVALUATING EPIDEMIOLOGICAL STUDIES

CRITERIA	
GENERAL:	
1.	Study is peer-reviewed.
2.	Study is written in English.
3.	Study measures exposure to at least one of the following pollutants: O ₃ , PM _{2.5} , PM ₁₀ , NO _x , SO ₂ ,
4.	Preference given to studies or groups of studies that significantly advance our understanding of the relationship between air pollution exposures and mortality and morbidity endpoints, including those endpoints previously quantified by the SCAQMD in its Air Quality Management Plans as well as new endpoints.
5.	Study was published within the following timeframes: <ul style="list-style-type: none"> a. PM_{2.5}/PM₁₀: 2012 - present b. NO₂: 2012 - present c. O₃: 2007 - present d. SO₂: 2003 - present
GEOGRAPHY AND STUDY POPULATION:	
6.	Study measures exposures at or near ambient levels found in the South Coast Air Basin. Order of preference of study location: <ul style="list-style-type: none"> a. South Coast Air Basin (Los Angeles, Orange, Riverside, and San Bernardino Counties) b. Within State of California c. Within Western United States d. Within United States or Canada
7.	Study uses study population with similar characteristics as found in Los Angeles, Orange, Riverside, and San Bernardino counties.
STUDY DESIGN:	
8.	Study is population-based, preferably using cohort or case-control epidemiological study designs. Controlled human exposure studies may be evaluated for supporting evidence, or in the absence of relevant epidemiology. Animal and in-vitro studies excluded.
9.	Study controls for factors that may obscure the true concentration-response relationship, including selection bias, misclassification, recall bias, confounding (including by other pollutants), effect modification, mortality displacement, loss to follow-up, etc.
10.	Study appropriately assesses any potential lag between exposure and outcomes.
11.	Study appropriately assesses any potential exposure thresholds for health outcomes.
12.	Study clearly presents information about uncertainty in results to facilitate evaluation and comparison with other studies.
13.	Prefer studies that assess changes in the risk of incidence of disease, rather than exacerbation of existing cases or changes in symptoms.

RESULTS

In this section, we present the results of our research, first presenting baseline information on endpoints and functions used previously and current weight of evidence determinations about causality by EPA, and then presenting the results of our supplemental literature review.

ENDPOINTS AND FUNCTIONS USED IN 2012 SOCIOECONOMIC REPORT

PM MORTALITY ENDPOINTS AND STUDIES

Adult Mortality

The prior SES Assessment estimated reductions in premature mortality expected to result from reductions in long-term (i.e., annual average) PM_{2.5} concentrations.¹ SCAQMD evaluated a number of mortality concentration-response functions, including several specific to the Los Angeles area, ultimately basing their estimates on the Los Angeles-specific estimates from the Krewski et al. 2009 ACS reanalysis.

- **Krewski et al. (2009)** conducted an extended analysis of the American Cancer Society cohort (followed for 18 years, 1982-2000). This study produced national mortality estimates as well as specific estimates for the Los Angeles metropolitan area, covering Los Angeles, San Bernardino, Ventura, Riverside, and Orange counties. Authors estimated exposure concentrations in three ways: a random effects model, a land-use regression (LUR) model, and kriging. The two latter techniques allowed authors to interpolate missing exposure values based on monitored data. The exposure models incorporated data from 23 PM_{2.5} monitors and 42 O₃ monitors in the Los Angeles metropolitan area. Forty-four covariates were assessed, including information on smoking and neighborhood factors such as income, race, education, and unemployment. The 2012 Socioeconomic Report used the relative risk of 1.17 for all-cause mortality per each 10 µg/m³ change in PM_{2.5} based on the kriging model for the Los Angeles area. This paper also calculated the concentration-response function for ischemic heart disease (IHD), cardiopulmonary disease (CPD), lung cancer, digestive cancer, other cancers, endocrine disorders, diabetes, digestive disorders, male accidents, female accidents, and all other causes.

¹ While evidence linking short-term (i.e., daily) PM_{2.5} exposures with premature mortality is also strong, estimating both impacts in the same analysis would likely lead to double-counting of the mortality, as the short-term effects are at least partially captured in the long-term mortality signal observed in the literature.

- **Jerrett et al. (2005)** analyzed the same dataset, focusing only on the ACS cohort in Los Angeles, California. This cohort study included nearly 23,000 subjects in the Los Angeles metropolitan area from 1982-2000 (with nearly 6,000 deaths) and used the same 44 individual confounders as in Krewski et al. (2009). The primary difference between Krewski et al. was the specifics of the exposure modeling. Authors developed a combined kriging and multiquadric model based on 2000 data from 23 state and local PM_{2.5} monitoring stations. This model provided concentration data for each 25m grid cell and authors assessed PM_{2.5} exposure at the ZIP code level. . Authors also developed a similar O₃ model based on 42 monitoring stations and assessed distance to freeways. This paper found the same relative risk (1.17) per 10 µg/m³ change in PM_{2.5} as for Krewski et al. This study also considered the same 44 covariates as in Krewski et al. (2009). The same mortality endpoints as in Krewski et al. were analyzed.
- **Laden et al. (2006)** extended follow-up to the Harvard Six Cities cohort study. PM_{2.5} exposure was assessed from 1979-1988. For each 10 µg/m³ increase in PM_{2.5}, the study found rate ratios for:
 - Overall mean exposure: 1.16; 95% confidence interval [CI], 1.07–1.26)
 - Exposure in the year of death: 1.14; 95% CI, 1.06–1.22
 - Lung cancer mortality: 1.27; 95% CI, 0.96–1.69
 - Cardiovascular mortality: 1.28; 95% CI, 1.13–1.44.

Infant Mortality

- Using a cross-sectional study design, **Woodruff et al. (1997)** assessed post-neonatal infant mortality. The study included about 3.6 million infants from 1989-1991 over 86 metropolitan areas in U.S. Authors obtained exposure data from the U.S. Environmental Protection Agency for the years 1999-2002. The analysis matched births to monthly average county-level exposures over the first two months of each infant's life. The infant mortality odds ratio for PM₁₀ exposure was 1.10 (95% CI, 1.04, 1.16).

PM MORBIDITY ENDPOINTS AND STUDIES

The previous SES Assessment quantified the morbidity endpoints for PM exposure listed in Exhibit 2 (derived from Figure 3-4 in the 2012 SES Assessment). We were able to confirm the function used by SCAQMD in 2012 for acute myocardial infarction. For the remainder of the categories, the EPA default sources for the health impact functions for these endpoints are listed in Exhibit 2; because BenMAP was used to conduct the prior analysis, we assume that at least one of the listed studies was used for each endpoint or that results from all the default studies were pooled to derive estimates in each category.

EXHIBIT 2. HEALTH ENDPOINTS FROM 2012 SES ASSESSMENT

ENDPOINT GROUP	ENDPOINT	AUTHOR	LOCATION
Acute Bronchitis		Dockery et al., 1996	
Asthma Exacerbation	Cough, shortness of breath, wheeze	Ostro et al, 2001	Los Angeles, CA
	Cough, Shortness of breath	Mar et al., 2004	Spokane, WA
Acute Myocardial Infarction	Acute Myocardial Infarction, nonfatal	Peters et al., 2001	Boston, MA
		Pope et al., 2006	Greater Salt Lake City, UT
		Sullivan et al., 2005	King County, WA
		Zanobetti and Schwartz, 2006	Greater Boston Area
		Zanobetti et al., 2009	
Hospital Admissions, Cardiovascular	All CVD (except MI)	Moolgavkar 2000 and 2003 are from LA	Los Angeles, CA
		Bell et al., 2008	202 U.S. Counties
		Peng et al., 2008	108 U.S. Counties
		Peng et al., 200	119 U.S. Communities
		Zanobetti et al., 2009	26 U.S. Communities
Hospital Admissions, Respiratory	All Respiratory	Zanobetti et al., 2009	26 U.S. Communities
ER Visits, Respiratory	Asthma	Mar et al., 2010	Tacoma, WA
		Norris, 1999	Seattle, WA
		Slaughter et al., 2005	Spokane, WA
Lower Respiratory Symptoms		Schwartz and Neas, 2000	6 U.S. Cities
Upper Respiratory Symptoms		Pope et al., 1991	Utah Valley
Minor Restricted Activity Days		Ostro and Rothschild, 1989	
Work Loss Days		Ostro, 1987	Nationwide

EPA CAUSALITY DETERMINATIONS FROM 2009 INTEGRATED SCIENCE ASSESSMENT FOR PM

U.S. EPA's Integrated Science Assessment (ISA) for PM, last published in 2009, discusses the weight of evidence of PM's role in causing the mortality and morbidity endpoints. EPA uses the definitions in Exhibit 3 for its causality determinations.

EXHIBIT 3. EPA PM ISA SUMMARY

Table 1-3. Weight of evidence for causal determination.

Determination	Health Effects	Ecological and Welfare Effects
CAUSAL RELATIONSHIP	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures. That is, the pollutant has been shown to result in health effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example: a) controlled human exposure studies that demonstrate consistent effects; or b) observational studies that cannot be explained by plausible alternatives or are supported by other lines of evidence (e.g., animal studies or mode of action information). Evidence includes replicated and consistent high-quality studies by multiple investigators.	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures. That is, the pollutant has been shown to result in effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. Controlled exposure studies (laboratory or small- to medium-scale field studies) provide the strongest evidence for causality, but the scope of inference may be limited. Generally, determination is based on multiple studies conducted by multiple research groups, and evidence that is considered sufficient to infer a causal relationship is usually obtained from the joint consideration of many lines of evidence that reinforce each other.
LIKELY TO BE A CAUSAL RELATIONSHIP	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures, but important uncertainties remain. That is, the pollutant has been shown to result in health effects in studies in which chance and bias can be ruled out with reasonable confidence but potential issues remain. For example: a) observational studies show an association, but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or b) animal toxicological evidence from multiple studies from different laboratories that demonstrate effects, but limited or no human data are available. Evidence generally includes replicated and high-quality studies by multiple investigators.	Evidence is sufficient to conclude that there is a likely causal association with relevant pollutant exposures. That is, an association has been observed between the pollutant and the outcome in studies in which chance, bias and confounding are minimized, but uncertainties remain. For example, field studies show a relationship, but suspected interacting factors cannot be controlled, and other lines of evidence are limited or inconsistent. Generally, determination is based on multiple studies in multiple research groups.
SUGGESTIVE OF A CAUSAL RELATIONSHIP	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but is limited because chance, bias and confounding cannot be ruled out. For example, at least one high-quality epidemiologic study shows an association with a given health outcome but the results of other studies are inconsistent.	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but chance, bias and confounding cannot be ruled out. For example, at least one high-quality study shows an effect, but the results of other studies are inconsistent.
INADEQUATE TO INFER A CAUSAL RELATIONSHIP	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quantity, quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an effect.	The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an effect.
NOT LIKELY TO BE A CAUSAL RELATIONSHIP	Evidence is suggestive of no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering susceptible populations, are mutually consistent in not showing an effect at any level of exposure.	Several adequate studies, examining relationships with relevant exposures, are consistent in failing to show an effect at any level of exposure.

EXHIBIT 4. EPA'S DEFINITIONS FOR CAUSAL DETERMINATIONS FOR PM-RELATED HEALTH ENDPOINTS

Table 2-6. Summary of PM causal determinations by exposure duration and health outcome.

Size Fraction	Exposure	Outcome	Causality Determination
PM _{2.5}	Short-term	Cardiovascular Effects	Causal
		Respiratory Effects	Likely to be causal
		Central Nervous System	Inadequate
		Mortality	Causal
	Long-term	Cardiovascular Effects	Causal
		Respiratory Effects	Likely to be Causal
		Mortality	Causal
		Reproductive and Developmental	Suggestive
		Cancer, Mutagenicity, Genotoxicity	Suggestive
PM _{10-2.5}	Short-term	Cardiovascular Effects	Suggestive
		Respiratory Effects	Suggestive
		Central Nervous System	Inadequate
		Mortality	Suggestive
	Long-term	Cardiovascular Effects	Inadequate
		Respiratory Effects	Inadequate
		Mortality	Inadequate
		Reproductive and Developmental	Inadequate
		Cancer, Mutagenicity, Genotoxicity	Inadequate

Exhibit 4 reproduces the table from the EPA 2009 PM ISA that summarizes EPA's findings of causality for each PM health endpoint evaluated. It shows that both short- and long-term PM exposure causes effects to the cardiovascular system, increases mortality, and likely affects the respiratory system. It may also impact pregnancy and development, and may be linked to cancer risk. We will recommend health endpoints to include in the 2016 socioeconomic assessment based on consideration of EPA's assessment of causality in its most recent ISA documents combined with the additional evidence we identified in our literature review.

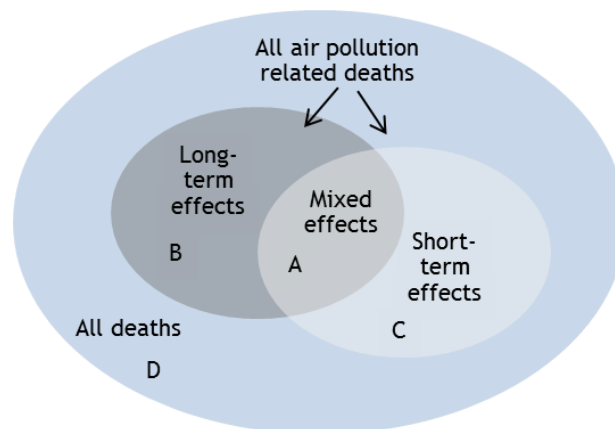
PM LITERATURE REVIEW FINDINGS

We discuss in the following two sections the results of our supplemental literature review for health effects of PM_{2.5} published since 2012. We first discuss studies linking PM_{2.5} and mortality, and then discuss studies linking PM_{2.5} with various morbidity endpoints. A summary table listing details on all studies found in our review can be found in Appendix A.

LITERATURE REVIEW FINDINGS: PM_{2.5} AND MORTALITY

We found 27 studies published since 2012 that assessed the relationship between mortality and PM_{2.5} exposure and were conducted in the U.S. or Canada. Eleven of the 27 studies focused on changes in daily mortality associated with short-term exposures to PM; 14 focused on mortality impacts of long-term PM exposures, and two (Kloog et al, 2013 and Shi et al. 2015) addressed both. Collectively, these studies support the existing weight of evidence determination by EPA regarding a causal association between PM_{2.5} exposure and mortality due to both short- and long-term exposure. However, we focus our attention on the long-term studies for two reasons. First, estimating benefits for both short- and long-term endpoints is likely to double count avoided mortality benefits because the long-term studies would be expected to capture at least some of the mortality increases due to short term PM fluctuations, in addition to PM-related mortality resulting from development of PM-related chronic disease and frailty (Kunzli et al., 2001; see Exhibit 5). Thus, selection of the long-term exposure studies should provide a better estimate of the overall mortality impact. The decision to focus on long-term mortality is also consistent with the 2012 Socioeconomic Analysis and thus would allow for comparisons across AQMPs, if desired.

EXHIBIT 5. **DIAGRAM ILLUSTRATING DEATHS CAPTURED BY LONG-TERM AND SHORT-TERM
EPIDEMIOLOGICAL STUDIES**



CATEGORY OF CASES	IMPACT OF AIR POLLUTION	
	UNDERLYING FRAILTY DUE TO AIR POLLUTION	OCCURRENCE OF DEATH (EVENT) TRIGGERED BY AIR POLLUTION
A	Yes	Yes
B	Yes	No
C	No	Yes
D	No	No

Graphic illustration of deaths due to ambient air pollution in a population, including cases related to both long-term and short-term air pollution. Exposure may affect the occurrence (event) of death ("short-term effects") and/or increase the underlying frailty in the population ("long-term effects"), leading to a shortening of lifetime. Circle sizes do not reflect relative effects. (Adapted from Kunzli et al., 2001).

We proceeded to narrow down the 16 studies that addressed long-term PM mortality based on the types of results they presented. Three were excluded from further consideration because they focused exclusively on specific causes of death: Brook et al, 2013 (diabetes mortality); Gan et al, 2013 (COPD-related mortality); and Kravchenko et al, 2014 (respiratory mortality). Two other studies were excluded because they were designed primarily to study effect modification of the PM-mortality association: Kiomourtzoglou et al, 2015 (effect modification by particle composition); Pope et al, 2015 (modification by cardiometabolic disorders).

Geographic Scope

The geographic scope of the remaining 11 studies shown in Exhibit 6 ranged from effects estimated in single cities to national-level estimates in the US and Canada. From this list, we prioritized studies conducted in the U.S. that reported either Los Angeles-specific estimates, California-specific estimates, or national-level estimates of mortality impacts based on multi-city studies that included cities from the Western U.S. based on data from over one hundred cities across the United States. Seven studies reported results from national-level analyses; most of these studies looked at dozens of U.S. cities (see Exhibit 3). Four studies focused on effects of PM_{2.5} exposures on populations within California and/or within LA specifically and are summarized below.

In a study funded by the California Air Resources Board, **Garcia et al. (2015)** looked at the relationship between mortality and long-term PM_{2.5} exposures in both rural and urban locations in California. This cross-sectional study focused on all Californian adults who died in 2006 and who were at least 65 years of age. Mortality endpoints included cardiovascular disease, ischemic heart disease, cardiopulmonary disease, and all-cause (non-accident). Monthly averages of ambient PM_{2.5} were calculated from 116 stations in California's National, State, and Local Air Monitoring Network and in Interagency Monitoring of Protected Visual Environments network from 2000-2006. ZIP code –level averages were calculated via three exposure models (closest monitor, inverse distance weighting, and kriging). The average PM_{2.5} concentrations were just over 10 µg/m³ in rural areas and just over 15 µg/m³ in urban areas. The study showed that the relative risk of mortality was greater in rural areas, but that a relationship between long-term PM exposure and mortality exists in both rural and urban areas. However, authors state that other confounding factors may account for this discrepancy, including arrival times for emergency responders, health behaviors, and health knowledge. This study did not control for smoking behaviors. We do not recommend its use in the SES Report because the study only evaluates outcomes for one year, only includes an elderly population, and does not control for tobacco use.

Jerrett et al. (2013) is a further extended follow-up of the American Cancer Society prospective cohort study, which is the same cohort used in Krewski et al. (2009) and Jerrett et al. (2005). As with the 2005 paper, this study focused solely on those individuals that reside in California. However, while the 2009 analysis assigns exposure at the ZIP code level, the 2013 analysis assigns exposure based on home residence using land-use regression models based on 112 stations measuring PM_{2.5} from 1998 to 2002, 138 stations measuring NO₂, and 262 stations measuring O₃. This approach provides

finer-scale exposure modeling than in the previous paper. The mean $PM_{2.5}$ exposure reported was $14.09 \mu\text{g}/\text{m}^3$ and the maximum was $25.09 \mu\text{g}/\text{m}^3$. Because mortality is higher outside of metropolitan areas (but air pollution generally lower), Jerrett controlled for this potentially confounding variable in addition to a similar suite of factors previously controlled for in 2005. They analyze exposures to $PM_{2.5}$, NO_2 , and O_3 for several causes of death, including CVD, IHD, stroke, respiratory disease, lung cancer, as well as all-cause mortality. $PM_{2.5}$ exposure was positively associated with all-cause mortality, and with CVD, and IHD-related deaths. The authors report an all-cause relative risk estimate for the state of California of 1.060 (1.003 – 1.120), which is similar to the national level ACS estimate of 1.065 (1.035 – 1.096), and they report an updated LA specific estimate for 1.104 (0.968 – 1.260). This estimate, while lower than that of Krewski et al., 2009 and Jerrett et al, 2005 continues to indicate higher impacts in the LA area than in California or in the nation as a whole.

Thurston et al. (2015) analyzed data from over half a million individuals from six U.S. states plus Atlanta and Detroit, including about 160,000 in California who were part of the National Institutes of Health/AARP Diet and Health cohort. Subjects were 50-71 years old. The study collects information on numerous covariates, including diet, exercise, smoking, education, and race. Contextual socioeconomic variables are also available at the census tract level from the NIH-AARP study (NIH-AARP, 2006). Exposure data was estimated using a land-use regression model based on U.S. EPA's Air Quality System for each census tract. Authors calculated hazard ratios for all-cause, respiratory, and CVD mortality for the U.S. and for California. Average mean $PM_{2.5}$ levels were $12.2 \mu\text{g}/\text{m}^3$ nationally and $10.4 \mu\text{g}/\text{m}^3$ in California. Results are similar to Jerrett et al. 2013 and Krewski et al, 2009 overall, though slightly lower than Jerrett et al. 2013 for California. For the U.S. results, concentration-response are broken down by smoking status, age, gender, and educational attainment. Results appear robust to alternative model specifications allowing for time varying exposure estimates. The list below contains the California-specific results.

- CVD: 1.10; 95% CI, 1.05, 1.16 for each $10 \mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$.
- All-cause: 1.02; 95% CI (0.99, 1.04)
- Respiratory: 1.01; 95% CI (0.93, 1.10)

Ostro et al. (2015) analyzed constituents of $PM_{2.5}$ on health outcomes from the California Teachers Study (CTS), a prospective cohort of over 130,000 active and retired female teachers. This study assessed the effects of $PM_{2.5}$ exposures to CTS participants ages 30 and over between 2001-2006. It controlled for smoking, second-hand smoke exposure, alcohol use, physical activity, fiber and calorie intake, menopausal status and use of hormones, family health history, and aspirin use. This paper used modeled exposure data from the University of California Davis/California Institute of Technology Source Oriented Chemical Transport model. Authors fitted Cox proportional hazards models; as a sensitivity analysis, they reran them to include variables to control for potential residential confounding, including Census data on poverty, educational attainment, income, percent unemployed, and racial make-up of neighborhood. These

variables are all group-level indicators of socioeconomic and environmental factors that could also be associated with individual-level health outcomes. Authors ran a series of two pollutant models for IHD. Their findings indicate that several constituents of PM_{2.5} and ultrafine PM are significantly associated with cardiovascular (CVD), ischemic heart disease (IHD), and all-cause mortalities. High sulfur and nitrate content of PM_{2.5} was associated with CVD and IHD mortality and sulfur was additionally associated with all-cause mortality. IHD mortality was also associated with PM_{2.5} mass, copper, elemental carbon, secondary organic aerosols, gas- and diesel-fueled vehicles, meat cooking, and high-sulfur fuel combustion. Because results are given only for constituents of PM, and not for overall PM and because of the fact that cohort was limited to a specific subgroup, female teachers, we do not recommend using this study to develop concentration response function for the SES Assessment.

EXHIBIT 6. SUMMARY OF LONG-TERM $PM_{2.5}$ -ASSOCIATED MORTALITY STUDIES.

CITATION	TITLE	JOURNAL	POLLUTANT(S)	MORTALITY CAUSE	GEOGRAPHIC SCOPE	POPULATION
Crouse et al., 2012	Risk of Nonaccidental and Cardiovascular Mortality in Relation to Long-term Exposure to Low Concentrations of Fine Particulate Matter: A Canadian National-Level Cohort Study	Environmental Health Perspectives	$PM_{2.5}$	All-cause/non-accidental; CVD; IHD	Canada	National sample of 2.1 million Canadian adults ≥ 25 years
Garcia et al., 2015	Association of Long-Term $PM_{2.5}$ Exposure with Mortality Using Different Air Pollution Exposure Models: Impacts in Rural and Urban California	International Journal of Environmental Health Research	$PM_{2.5}$	All-cause/non-accidental; CVD; CPD; IHD	Compares rural and urban locations in California	Individuals ≥ 65 years who died in 2006
Hart et al., 2015	The Association of Long-Term Exposure to $PM_{2.5}$ on All-Cause Mortality in the Nurses' Health Study and the Impact of Measurement-Error Correction	Environmental Health	$PM_{2.5}$	All-cause/non-accidental	United States	Participants in Nurses' Health Study, still alive in 2000
Jerrett et al., 2013	Spatial Analysis of Air Pollution and Mortality in California	Respiratory and Critical Care Medicine	$PM_{2.5}$, O_3 , NO_2	All-cause; CVD; IHD; Stroke, Respiratory; Lung cancer;	Extended follow-up of American Cancer Society cohort in California/Los Angeles	California adults from American Cancer Society Cancer Prevention II Study
Kloog et al. 2013	Long- and Short-Term Exposure to $PM_{2.5}$ and Mortality: Using Novel Exposure Models	Epidemiology	$PM_{2.5}$	All-cause; CVD; Respiratory	State of Massachusetts	State of Massachusetts

CITATION	TITLE	JOURNAL	POLLUTANT(S)	MORTALITY CAUSE	GEOGRAPHIC SCOPE	POPULATION
LePeule et al., 2012	Chronic Exposure to Fine Particles and Mortality: An Extended Follow-up of the Harvard Six Cities Study From 1974 to 2009	Environmental Health Perspectives	PM _{2.5}	All-cause;CVD; Lung cancer;COPD	Six cities in eastern and midwestern U.S. (Watertown, MA, Kingston and Harriman, TE, parts of St. Louis, MI, Steubenville, OH, Portage, Wyocena, and Pardeeville, WI, Topeka, KA)	Extended follow-up of U.S., Harvard Six Cities cohort
Ostro et al., 2015	Associations of Mortality with Long-Term Exposures to Fine and Ultrafine Particles, Species and Sources: Results from the California Teachers Study Cohort	Environmental Health Perspectives	PM, UF	All-cause; CVD; IHD; Respiratory	California	California Teachers Study Cohort; women >30 years
Shi et al, 2015	Low-Concentration PM _{2.5} and Mortality: Estimating Acute and Chronic Effects in a Population-Based Study	Environmental Health Perspectives	PM _{2.5}	All-cause	New England	Medicare population aged ≥ 65 in New England
Thurston et al., 2015	Ambient Particulate Matter Air Pollution Exposure and Mortality in the NIH-AARP Diet and Health Cohort	Environmental Health Perspectives	PM _{2.5}	All-cause; CVD; Respiratory	Six states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Detroit, MI and Atlanta, GA)	National Institutes of Health-AARP cohort; ages 50-71 years; includes California specific estimates

CITATION	TITLE	JOURNAL	POLLUTANT(S)	MORTALITY CAUSE	GEOGRAPHIC SCOPE	POPULATION
Villeneuve et al., 2015	Long-term Exposure to Fine Particulate Matter Air Pollution and Mortality Among Canadian Women	Epidemiology	PM _{2.5}	All-cause non-accidental; Coronary heart disease, cerebrovascular disease, CVD; nonmalignant respiratory disease; cancer; lung cancer	Canada	Participants in the Canadian National Breast Screening Study between 1980 and 1985
Weichenthal et al., 2014	Long-Term Exposure to Fine Particulate Matter: Association with Nonaccidental and Cardiovascular Mortality in the Agricultural Health Study Cohort	Environmental Health Perspectives	PM _{2.5}	All-cause/non-accidental; CVD; IHD; Cerebrovascular disease; Lung cancer	Iowa and North Carolina	Agricultural Health Study Cohort; rural populations
CVD=cardiovascular disease, CPD=cardiopulmonary disease, COPD= chronic obstructive pulmonary disease, IHD=ischemic heart disease						

LITERATURE REVIEW FINDINGS - PM_{2.5} MORBIDITY

In this section, we discuss the finding of our literature review for both the health endpoints previously evaluated in the 2012 Socioeconomic Report and potential new health endpoints to quantify in the 2016 analysis.

We identified 85 studies on PM and morbidity outcomes conducted in the United States or Canada since 2012. The geographic scope of these studies ranged from single-city to county-wide analyses. Thirteen studies were conducted within the state of California, with eight of those studies specifically focusing on areas in southern California. Twenty-three studies included data either from multiple states and cities across the United States or focused on areas in the western part of the country. Details on all morbidity studies identified can be found in Appendix A.

Existing Health Endpoints

In general, we found the literature we reviewed to be consistent with existing EPA opinions concerning causality published in the 2009 ISA. As a result, we continue to recommend quantification of the health endpoints evaluated for PM in the 2012 analysis, though not necessarily using the same studies.

The previous SES Assessment included the morbidity endpoints for PM exposure listed in Exhibit 2. We discuss below the endpoints where we identified additional studies conducted since 2012 in California, western U.S., or nationwide.

Acute Nonfatal Myocardial Infarction (MI)

Our literature review found one study of PM-related acute MIs published since 2012 within our geographic area of interest.

Ensor et al. (2013) conducted a case-crossover analysis of air pollution and out-of-hospital cardiac arrests based on EMS data from 2004 and 2011 in Houston, Texas and found that an increase of 6 $\mu\text{g}/\text{m}^3$ of PM_{2.5} two days prior was associated with a relative risk of cardiac arrest of 1.046 (1.012 – 1.082). Limitations of this study include use of citywide-averaged PM data and a lack of control for pre-existing conditions and risk factors. In addition, this study did not ascertain whether the cardiac arrest was fatal; therefore the outcome measure may be capturing some of the mortality impacts addressed elsewhere.

Asthma Exacerbation

Our literature review found one study of PM-related asthma exacerbation published since 2012:

Loftus et al. (2015) studied associations between PM_{2.5} and asthma exacerbations in children in a rural agricultural community in Washington State. The authors found that an interquartile increase in weekly PM_{2.5} of 6.7 $\mu\text{g}/\text{m}^3$ was associated with an increase in reported asthma symptoms, in particular wheezing, limitation of activities, and nighttime waking.

Nachman and Parker (2012) assessed the effect of a 10 $\mu\text{g}/\text{m}^3$ increase in annual average $\text{PM}_{2.5}$ on asthma prevalence and asthma exacerbation (asthma attack). The population was the 110,000 adult (≥ 18 years) respondents to the National Health Interview Survey (NHIS); 4,000 of these participants reported an asthma attack in the previous year. Kriged $\text{PM}_{2.5}$ concentrations at the Census block group level based on data from U.S. EPA's AirData System were used to measure exposure. The overall OR did not show an association between a 10 $\mu\text{g}/\text{m}^3$ increase in annual average $\text{PM}_{2.5}$ exposure and recent asthma attacks (OR of 0.90 (95% CI: 0.78, 1.03)). However, when the authors stratified results by race (Hispanic, non-Hispanic white, non-Hispanic black), a significant association was seen for non-Hispanic blacks (OR of 1.76, (95% CI: 1.07, 2.91)). This study controlled for age, sex, body mass index, smoking, ethnicity, education, and urbanicity.

Young et al. (2014) investigated the association between $\text{PM}_{2.5}$ exposure and the incidence of asthma, wheeze, and chronic cough in adult women (≥ 35 years) without symptoms or asthma diagnoses at the start of the study. Study participants were from the nationwide, 50,884 subject Sister Study, a cohort of women with one sister diagnosed with breast cancer but who do not have the disease themselves. $\text{PM}_{2.5}$ exposure estimates were based on a national kriging and land-use regression model for the year 2006. For each interquartile range of $\text{PM}_{2.5}$ (3.6 $\mu\text{g}/\text{m}^3$), the odds of developing asthma were 1.20 (95% CI: 0.99, 1.46). For developing wheeze, the OR was 1.14 (95% CI: 1.04, 1.26). Authors controlled for age, body mass index, race, education, occupational exposures, smoking, health insurance, and fiber consumption.

Cardiovascular Hospital Admissions

Our literature review found two studies of PM-related cardiovascular hospital admissions published since 2012:

Bell et al. (2015). Studied cardiovascular and respiratory hospital admissions in among Medicare beneficiaries 65 and older across 213 U.S. cities to evaluate whether the effect of short-term $\text{PM}_{2.5}$ exposures on hospital admissions in the U.S. varied by gender. Cause-specific respiratory and cardiovascular hospital admissions for 12.6 million individuals were evaluated using Bayesian hierarchical modeling for associations with daily county-level $\text{PM}_{2.5}$ from EPA AQS monitors. PM data came from monitoring sources and was adjusted for weather, day of the week, and temporal trends. Study controlled for gender, location, and season. Study was designed primarily to assess differences in risk by gender, but did report some total risk estimates. While hospital admissions overall increased by 0.25 percent (respiratory) and 0.65 percent (cardiovascular) per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ (same day exposure, lag 0), results stratified by region showed non-significant results in the West (33 counties).

Talbott et al. (2014) conducted a time-stratified case-crossover analysis with logistic regression to evaluate the association of daily $\text{PM}_{2.5}$ levels on cardiovascular disease hospital admissions (ICD-9 350-359). Outcome information for 2001-2008 was obtained from the CDC Environmental Public Health Tracking (EPHT) network for seven states

(Florida, Massachusetts, New Hampshire, New Jersey, New Mexico, New York, and Washington) and regressed against modeled daily $PM_{2.5}$ estimated at zip code centroids and linked to the zip code of patient residence. Overall results from this study are likely weighted too heavily towards eastern U.S. locations to be appropriate for use in Los Angeles. While this study does report results for Washington state; we do not believe that these results should replace or supplement local Los Angeles data in the current studies (Moolgavkar, 2000, 2003) informing BenMAP concentrations response functions for cardiovascular hospital admissions.

Chronic Bronchitis

Our literature search found one study (Nachman and Parker, 2012) that analyzed the relation of PM with this endpoint based on self-reported prevalence in the National Health Interview Study; the authors found no association of PM with chronic bronchitis.

Respiratory Emergency Room Visits

Our literature search found one study (Rodopoulou et al., 2014) that analyzed the relation of PM with this endpoint during severe air pollution events involving windblown dust and wildfires in New Mexico. This study does not appear to be relevant for the Socioeconomic Analysis of benefits because of its focus on extreme air events.

Respiratory Hospital Admissions

Our literature review found two studies of PM-related respiratory hospital admissions.

Delfino et al. (2014) assessed asthma-related hospital encounters (hospital admissions and emergency department visits) in a case-crossover study of over 11,000 children ages 0-18 years in Orange County, CA. This study measured $PM_{2.5}$, UFP, NO_2 , and CO exposures. , Mean $PM_{2.5}$ concentrations were $14.5 \mu g/m^3$; however, one limitation of this study is that all $PM_{2.5}$ measurements came from a single monitor. Authors calculated effects from zero to seven day lags in exposure and accounted for subjects that had more than one hospital encounter in a seven day stretch. Weather, age, sex, race, and insurance status were assessed. Both the warm and cool seasons showed positive associations with $PM_{2.5}$ exposures. We consider a lag of three days to be the most appropriate assessment of the effects of $PM_{2.5}$ exposure. For a three day lag in the warm season, the interquartile range of $PM_{2.5}$ ($15.4 \mu g/m^3$) lead to an 8.00% increase in asthma-related hospital encounters (95% CI 1.2%, 15.22%). In the cool season, the point estimate is 3.48% (95% CI -0.77%, 7.92).

Delamater et al. (2012) is an ecological study of asthma hospitalizations in Los Angeles County. Authors developed a kriging model based on monitor data in Los Angeles, CA to estimate exposures within 3 km x 3 km grid cells. They used data from OSHPD and interpolated annual state population data to calculate the average daily hospitalization rate by month. The study found that a one percent change in monthly average $PM_{2.5}$ was associated with a 0.11% (95% critical interval=0.01, 0.21) increase in hospitalizations.

LITERATURE REVIEW RESULTS: NEW ENDPOINTS

We identified studies addressing a wide array of health endpoints not previously evaluated by SCAQMD, including the following:

- Pregnancy outcomes
 - Birth weight
 - Low birth weight (generally <2500 g)
 - Very low birth weight (<1500 g)
 - Small for gestational age
 - Mean birth weight at term birth
 - Pre-term birth
 - Stillbirth
 - Birth defects
 - Gestational diabetes mellitus
 - Hypertensive disorders of pregnancy
- Asthma incidence
 - One each on asthma onset in children and in adult women
- Stroke and cerebrovascular disorders
- Other health outcomes including
 - appendicitis
 - anxiety and depression
 - autism
 - breast cancer survival
 - diabetes
 - endometriosis
 - ED visits for non-specific abdominal pain
 - leukemia in adults
 - Parkinson's disease (one of these studies also reports time to first admission for dementia and Alzheimer's disease)
 - rheumatoid arthritis
 - uterine fibroids

Most of the endpoints in the Other category above consisted of only a single study; for endpoints where we found multiple studies (Parkinson's, rheumatoid arthritis, etc.) results either found no association or were mixed. Similarly, within the Pregnancy Outcomes, the most consistently studied outcome was Low Birth Weight, including several studies in the LA area. We focus below on that endpoint, as well as stroke, asthma incidence, and autism.

Low Birth Weight

This review found five California-based studies, one nationwide-wide study, and one meta-analysis on air pollution and low birth weight (LBW). These studies generally define LBW as <2,500g and full-term pregnancies as >37 weeks. These studies typically controlled for season of birth, gestational age, mother's age, race, and socioeconomic factors such as educational attainment and/or income. The average shifts in birth weight are all very small and under one ounce. Overall, these studies provide evidence that exposure to PM_{2.5} during pregnancy, especially higher exposures over an entire pregnancy, can increase the risk of lower birth weight. Below we summarize these seven studies. We include two pre-2012 studies as they assess populations in Los Angeles and California.

- **Basu et al. (2014)** assessed ZIP code-level PM_{2.5} exposure for nearly 650,000 term births in California. Results were adjusted for a number of socioeconomic status factors, gestational age, mother's age, sex, and month of birth. Birth weight decreased by 7g (95% CI 4, 9) per 7.6 µg/m³ increase in PM_{2.5} mass (interquartile range). This study breaks down results by PM constituent; however due to the difficulty in modeling those exposures those results are not reported here.
- **Laurent et al. (2014)** studied over 960,000 births in Los Angeles County and assessed exposure to PM_{2.5} via Bayesian kriging using 4km² gridcells. Over the entire pregnancy, a 2.5% increase in the risk of LBW was associated with an interquartile range (5.82 µg/m³ increase) in PM_{2.5}. This study controlled for many of the same factors as previously mentioned, although did not control for smoking.
- **Morello-Frosch et al. (2010)** found a decrease in birth weight of 12.8g (95% CI 11.3, 14.3) per 10 µg/m³ PM_{2.5} for full-term births (>37 weeks). This study looked at over 3.5 million births over 10 years in California. Air pollution was averaged by Census tract and ZIP code. Authors state a decrease of this magnitude is unlikely to affect the health of an individual infant, but could have population-level impacts due to the widespread exposure to air pollutants across California.
- **Ritz et al., (2007)** conducted a case-control study of about 58,000 births in Los Angeles County. About 2,500 mothers were interviewed to assess confounders. Air pollution exposure was based on ZIP code. For women exposed to average PM_{2.5} over 21.36 µg/m³, odds of a low birth weight baby increased 10% (95% CI 1.01, 1.20) (interviewed cohort) to 29% (95% CI 1.00, 1.67) (overall cohort). This study adjusted for mother's age, race, education, season, and for the interviewed cohort, smoking, alcohol use, and marital status.
- **Trasande et al. (2013)** assessed the impact of air pollutants on low birth weight across the U.S. This study used the Kids Inpatient Database (KID), which records in-hospital births from up to 38 states (depending on year). Authors used pollutant concentrations from the U.S. EPA Aerometric Information Retrieval System (AIRS) coupled with random subsampling of over 2.6 million births in

KID for 2000, 2003, and 2006. Authors controlled for gestational age, birth month, gender, race, socioeconomic variables. They were able to link one third of births in KID to AIRS data. Single pollutant models of PM_{2.5} showed an association with odds of LBW (OR of 1.10 (95% CI of 1.06, 1.14)), very LBW (OR of 1.08 (95% CI of 1.05, 1.11)), pre-term LBW (OR of 1.09 (95% CI of 1.04, 1.14)), and LBW for term births (OR of 1.12 (95% CI of 1.08, 1.16)). In the multi-pollutant models, the 62,906 births with birth weight as a continuous variable show no significant association with air pollutants was found. However, for the 82,379 births with categorical data (i.e., <2,500g and <1,500g), the multi-pollutant models show that each µg/m³ of PM_{2.5} led to a 9.3% and 7.2% increase in the odds of LBW.

- **Wilhelm et al.** (2012) studied nearly a quarter million births in the South Coast Air Quality Management District as part of the Multiple Air Toxics Exposure Study (MATES III). Exposure was assessed using monitors within five miles of a woman's home address and also from a land-use regression model. Authors found a 5% increase in LBW for each 2.4 µg/m³ PM_{2.5} (from diesel and gasoline combustion-related PM_{2.5}) increase over the entire pregnancy. Point estimates for each trimester were similar. This study controlled for gestational age, mother's age, race, socioeconomic factors, and prenatal care, but not for smoking. Authors do not report an overall PM_{2.5} estimate; the adjusted odds ratios by PM type are:
 - Elemental carbon PM_{2.5}: 1.05 (0.97, 1.14)
 - Diesel PM_{2.5}: 1.06 (0.99, 1.14)
 - Gasoline PM_{2.5}: 1.07 (0.97, 1.18)
 - Geological PM_{2.5} (i.e., road dust): 1.05 (0.97, 1.14)
- In 2015, **Zhu et al.** conducted a meta-analysis of 25 epidemiological studies on the risk of low birth weight (LBW), pre-term birth (PTB), small for gestational age (SGA), and stillbirth from PM_{2.5} exposure over the entire pregnancy. All outcomes except stillbirth were significantly associated with PM_{2.5} exposure, with an average of 14.6g drop in expected birth weight. Results for each of the three trimesters showed no effect on PTB or stillbirth and no effect on weight for the first trimester. The odds ratios for exposure during the entire pregnancy were:
 - LBW: 1.05 (1.02, 1.07)
 - PTB: 1.10 (1.03, 1.18)
 - SGA: 1.15 (1.10, 1.20)

Stroke

Our literature review found one study which assessed the risk of stroke in dozens of cities across the U.S. This meta-analysis by **Shin et al.** (2014) pooled 20 epidemiological studies which reported risk ratios (RR) for strokes following long and short-term PM_{2.5} exposures. Authors used both frequentist and Bayesian methods to pool studies. Four

studies (four RRs) involved long-term exposure and 16 studies (221 RRs) involved short-term exposures. Authors focused on single-pollutant models in each paper to more easily pool across a wider number of studies. The four long-term studies used cohorts involving Medicare recipients, the Women's Health Initiative (Miller et al., 2007), the California Teacher's Cohort (current and former female public school teachers), and patients at primary care centers in England. The pooled risk estimate from the long-term studies was 1.05 (95% CI= 1.00, 1.13). Of the 16 short-term studies, 15 focused on one city each and one (Dominici et al., 2006) reported 202 single-city RR across its U.S. multi-city assessment. Authors arrived at a pooled estimate of 1.05 (95% CI = 1.01, 1.09) for each 10 $\mu\text{g}/\text{m}^3$ increase in short-term $\text{PM}_{2.5}$ exposure. Results were similar regardless of the specific pooling method used.

Asthma incidence

We found two studies addressing asthma incidence, one addressing onset in adults and the other addressing onset in children.

Young et al. (2014) studied onset of asthma in a cohort from The Sister Study, a U.S. cohort study of risk factors for breast cancer and other health outcomes ($n = 50,884$) in sisters of women with breast cancer (enrollment, 2003–2009). The authors evaluated the association between ambient air pollution exposures ($\text{PM}_{2.5}$ and nitrogen dioxide, NO_2) and development of asthma and incident respiratory symptoms. Specific health endpoints examined included incident self-reported wheeze, chronic cough, and doctor-diagnosed asthma in women without baseline symptoms. Study controlled for factors including age, BMI, daily fiber consumption, baseline smoking status, education, race, second-hand smoke exposure, health care coverage, and occupational exposure to dust and fumes.

Average PM exposure level in population studied: Annual average (2006) ambient $\text{PM}_{2.5}$ and NO_2 concentrations were estimated at participants' addresses, using a national land-use/kriging model incorporating roadway information. The medians (and interquartile ranges) for estimated exposures at participant locations were 10.8 mg/m^3 (3.6 mg/m^3) for $\text{PM}_{2.5}$ and 9.3 ppb (5.8 ppb) for NO_2 .

The results of this large nationwide cohort study suggest that ambient $\text{PM}_{2.5}$ exposure or other related exposures may be involved in the development of respiratory symptoms, particularly wheeze, and incident asthma in women. Adjusted analyses included 254 incident cases of asthma, 1,023 of wheeze, and 1,559 of chronic cough. For an interquartile range (IQR) difference (3.6 mg/m^3) in estimated $\text{PM}_{2.5}$ exposure, the adjusted odds ratio (OR) was:

- 1.20 (95% confidence interval [CI] = 0.99–1.46, $P = 0.063$) for incident asthma
- 1.14 (95% CI = 1.04–1.26, $P = 0.008$) for incident wheeze.
- For NO_2 , there was evidence for an association with incident wheeze (OR = 1.08, 95% CI = 1.00–1.17, $P = 0.048$ per IQR of 5.8 ppb).
- Neither pollutant was significantly associated with incident cough.

Wendt et al., 2014 studied the impact of changes in ambient PM_{2.5}, ozone, and NO₂ on new-onset asthma in Medicaid-enrolled children in Harris County, Texas between 2005 and 2007 using a case-crossover design and conditional logistic regression. They found that new-onset asthma was more likely to occur following periods of higher exposures to all three pollutants in single-pollutant models; however only the ORs for ozone and NO₂ remained significant in multi-pollutant models.

Autism

This literature review found three studies on PM_{2.5} and autism in either California or nationwide. All three studies found positive associations with PM_{2.5}. Authors note that PM_{2.5} exposures may initiate changes in immune system function leading to the development of autism, but that the mechanism is still largely unknown.

Becerra et al. (2013) assessed the impact of PM_{2.5} exposure on the odds of developing autism for children living in Los Angeles. This study included 7,603 cases which were matched with 10 controls per case by sex, birth year, and gestational age. Exposure was measured via the nearest monitoring station and by a land-use regression model. For each interquartile range increase (4.68 µg/m³) in PM_{2.5}, authors found a 7% increase in autism in a single pollutant model (95% CI of 1.00, 1.15); this estimate increased to 15% in a two pollutant model with O₃ (95% CI of 1.06, 1.24). Results were adjusted by maternal age, education, race, maternal place of birth, type of birth, parity, insurance, and gestational age.

Raz et al. (2015) is a nested case-control study of births of participants in the Nurses' Health Study II. The study assessed air pollution exposure for 245 children with and 1,522 children without autism across the U.S. PM_{2.5} concentrations were based on previously developed spatiotemporal models based on U.S. EPA's Air Quality System (AQS). For each interquartile range increase in monthly average PM_{2.5} (4.42 µg/m³), the odds ratio of having autism was 1.57 (95% CI: 1.22, 2.03). PM_{2.5} exposures nine months prior to or after pregnancy were either weakly associated or null.

Volk et al. (2013) conducted a case-control study on children enrolled in the Childhood Autism Risks from Genetics and the Environment (CHARGE) study in California. The study included 279 autistic children and 245 without autism. PM_{2.5} exposures were assessed from interpolating all monitor data within 50 km of residence, with data from U.S. AQS and University of Southern California Children's Health Study. For every 8.7 µg/m³ increase in PM_{2.5}, the odds of having autism increased. For gestational exposures, the OR was 2.08 (95% CI: 1.93, 2.25) and for exposures during the first year of life the OR was 2.12 (95% CI: 1.45, 3.12) after adjusting for sex, ethnicity, parental education, maternal age, and prenatal smoking.

RECOMMENDATIONS

Exhibit 6 summarizes our recommended PM-related health endpoints for the 2016 Socioeconomic Analysis. In summary, we propose evaluation of the same endpoints evaluated in 2012 plus avoided incidence of hospital admissions for stroke in adults 65 and older. We also are expanding certain endpoint categories to include additional age groups or subpopulations from the studies we identified. Gray-highlighted rows indicate changes in recommended studies from the 2012 Socioeconomic Report.

Note that all C-R functions and related parameters will be developed in accordance with the EPA's BenMAP-CE User's Manual Appendix C (U.S. EPA, 2015). Specific functional forms and input parameters will be specified once study and risk model recommendations are finalized.

EXHIBIT 6. RECOMMENDED PM_{2.5}-RELATED HEALTH ENDPOINTS

ENDPOINT	POLLUTANT	STUDY	STUDY POPULATION
Premature Mortality			
Premature mortality—all-cause ^a	PM _{2.5} (annual avg)	Pooled estimate of Jerrett et al. (2013) LA Jerrett et al. (2005) LA Krewski et al. (2009) LA	>30 years
Infant mortality—all-cause	PM _{2.5} (annual avg)	Woodruff et al. (1997)	Infant (<1 year)
Chronic Illness			
Nonfatal myocardial infarction	PM _{2.5} (24-hour avg)	Pope et al., 2006; Sullivan et al., 2005; Zanobetti et al., 2009; Zanobetti & Schwartz, 2006	Adults (>18 years)?
Hospital Admissions			
Stroke, Ischemic	PM _{2.5} (24-hour avg)	Shin et al., 2014	>65 years
Respiratory	PM _{2.5} (24-hour avg)	Zanobetti et al, 2009, all respiratory	>65 years
Respiratory	PM _{2.5} (24-hour avg)	Moolgavkar (2000)—ICD 490-492, 494-496 (COPD, less asthma)	18-64 years

ENDPOINT	POLLUTANT	STUDY	STUDY POPULATION
Cardiovascular	PM _{2.5} (24-hour avg)	Moolgavkar (2003)—ICD 390-429 (all cardiovascular)	>64 years
Cardiovascular	PM _{2.5} (24-hour avg)	Moolgavkar (2000b)—ICD 390-429 (all cardiovascular)	20-64 years
Asthma-related ER visits and Hospital Admissions	PM _{2.5} (24-hour avg)	Delfino et al. 2014.	<18 years
Other Health Endpoints			
Acute bronchitis	PM _{2.5} (annual avg)	Dockery et al. (1996)	8-12 years
Lower respiratory symptoms	PM _{2.5} (24-hour avg)	Schwartz and Neas (2000)	7-14 years
Upper respiratory symptoms	PM _{2.5} (24-hour avg)	Pope et al. (1991)	9-11 years
Asthma exacerbation	PM _{2.5} (24-hour avg)	Pooled estimate: Ostro et al. (2001) (cough, wheeze, shortness of breath) Mar et al., 2004 (cough, shortness of breath)	6-18 years
Asthma exacerbation	PM _{2.5} (24-hour avg)	Young et al., 2014	>34 years
Minor restricted-activity days	PM _{2.5} (24-hour avg)	Ostro and Rothschild (1989)	18-64 years
Work loss days	PM _{2.5} (24-hour avg)	Ostro (1987)	18-64 years

PM MORTALITY

We recommend that SCAQMD use a pooled estimate of the Los Angeles-specific results from Krewski et al., 2009; Jerrett et al., 2005, and: Jerrett et al. 2013 to assess PM-associated adult mortality. All are high quality studies based on followup of the well-regarded ACS cohort that apply results from that study population to assess the mortality impacts at a finer spatial scale within the Los Angeles metropolitan area. Each successive study applies a finer resolution exposure assessment than the Jerrett et al., 2013 is an update of the Krewski analysis that estimates PM_{2.5} exposures at finer resolution than the previous analyses, while otherwise maintaining the previous studies' methodological strengths.

All three studies illustrate a larger mortality effect estimate in Los Angeles than is observed nationally, with the latter estimate finding a somewhat lower relative risk in LA than the 2005 and 2009 values. We also note that the latest Jerrett study also reports PM mortality estimates for the entire state of California that are consistent with both past work (Jerrett et al., 2005) and with the recently released study of PM mortality in the AARP cohort (Thurston et al., 2015). However, the Los Angeles all-cause mortality RR

of 1.104 (0.968 – 1.260) in Jerrett is not statistically significant, unlike the other two estimates. The authors note that sample sizes for the two Jerrett et al. studies differed due to restrictions related to the exposure assessment. It is possible this may be a contributing factor to the lack of significance. Nonetheless, we believe that the quality of the 2013 study overall, the consistency of its results with past and current estimates at the state level, its consistent cause-specific results for LA, and its consistent results for spatial trends of the PM mortality relationship warrant inclusion in the 2016 analysis. We believe a pooling of mortality estimates from the Krewski et al., 2009 function used in the 2012 Socioeconomic Analysis; a function based on the 1.17 (1.05 – 1.30) all-cause mortality RR from Jerrett et al., 2005; and a function based on the 1.104 (0.968 – 1.26) all-cause mortality RR from Jerrett et al., 2013 is a reasonable approach that makes best use of the most recent science for the Los Angeles area. We recommend using the Fixed or Random Effects Pooling mode for the BenMAP runs conducted with these CR functions; while fixed effects pooling seems intuitively plausible for combining these functions, this approach will allow for the use of a random effects approach if it is statistically supported.

Given the variation in the estimates between the first two studies and the 2013 study, uncertainty remains as to the true difference between the PM mortality impact in LA and elsewhere. Therefore, SCAQMD may wish to consider additional sensitivity analysis that uses the results from studies conducted at progressively larger geographic scales. That is, SCAQMD could apply a sensitivity analysis using a state level PM mortality estimate and also an estimate using a national-scale PM-mortality estimate.

We also recommend continued evaluation of infant mortality based on the Woodruff et al., 1997 study, based on no additional research on this endpoint being identified in our search.

PM MORBIDITY

For existing morbidity endpoints, we recommend using existing pre-2012 studies and BenMAP C-R functions for most of them, because for most endpoints we either found no new studies for endpoints or we do not find the latest studies we identified present a compelling case to replace existing C-R functions in BenMAP. We do, however, recommend that SCAQMD choose from among the default BenMAP studies in a manner that emphasizes results that are as geographically specific as possible. Thus, the existing studies we recommend in the table above are either conducted in the Los Angeles area (e.g., the Moolgavkar hospital admission studies), or in California and/or other western states, or represent an average U.S. estimate across a broad range of locations.² We excluded from our recommendations table studies conducted in a single location outside

² For respiratory hospital admissions for populations 65 and older, we recommend using the Zanobetti et al., derived C-R function, which is based on a nationwide analysis of impacts on hospital admissions for all respiratory causes. While the Moolgavkar Los Angeles study from 2000 provides an LA-specific estimate, that estimate is specific to COPD admissions. Therefore, we recommend using the more complete nationwide estimate in this case.

of the western U.S., unless no other studies were available. Where multiple studies are listed in the recommendations table, we propose these studies be pooled with equal weights, in the absence of compelling evidence to include one over the other.

For children's ER visits for asthma, we do not recommend using the Delamater et al. paper. We are uncertain about the strength of the association given the paper's reliance on monthly mean hospitalization rates that are derived based on the authors' own assumptions about interpolating annual population growth. We do recommend developing a function based on the work by Delfino et al. in Orange County for all hospital encounters (ER visits and admissions) for asthma in children using a seasonally pooled PM_{2.5} estimate for all subjects. We find this to be a strong, well-documented, locally applicable study whose strengths outweigh the limitations associated with the use of PM exposure data from a single monitor. We propose to pool the results of two season specific C-R functions based on the 3-day lag estimates for PM_{2.5}.

We also propose augmenting the asthma exacerbation endpoint category with a new C-R function based on a new study of asthma exacerbation in adults. We propose to use the fully-adjusted OR for incident wheeze in adult women from the Young et al. 2014 U.S. cohort study to assess changes in asthma exacerbation among this subpopulation.

For new endpoints, we propose to add a C-R function for hospital admissions for ischemic stroke based on the Shin et al. meta-analysis of long-term and short-term PM effects on stroke incidence. Although the Shin analysis was the only paper on PM and stroke we found published since 2012, the paper makes a compelling argument for including stroke as an endpoint. First, it cites a broad base of existing evidence to support a biological mechanism between PM and stroke, including the substantial evidence showing PM induces cardiovascular effects that contribute to stroke risk. Second, it presents robust meta-analysis results for both long-term and short-term exposures using both traditional frequentist and Bayesian approaches to combining study estimates. We recommend that a C-R function be developed for the short-term RR estimates for ischemic stroke. The short-term estimate is derived from a larger literature base than the long-term estimate, and ischemic stroke RR (1.05, 1.01 – 1.09 using the Gamma prior; 1.05, 0.99 – 1.14 using the normal prior) demonstrated the tightest confidence intervals across both frequentist and Bayesian approaches. We conclude that the use of the gamma-based estimate is justified given the likelihood of a causal relationship via the cardiovascular impacts of PM_{2.5}.

We are reserving judgment at this time regarding asthma incidence from PM mass exposure. We believe Young et al., 2014 is a strong study, and we particularly like its rigorous definition of asthma onset. However, given that there is very little other evidence linking PM with adult asthma onset, we are reluctant to recommend evaluating this endpoint for PM. We propose to re-evaluate this endpoint as part of our assessment of NO₂ associations.

We are not proposing to evaluate the Low Birth Weight endpoint at this time with respect to PM. While this continues to be a growing field of study and we discovered several

studies conducted in the Los Angeles area specifically that reported positive associations, we do not believe the results are yet consistent enough to warrant inclusion. For example, the Laurent study found positive associations with Low Birth Weight but did not control for the smoking; the Ritz study found effects only when exposure occurs over relative high PM threshold; and the Wilhelm study was not able to find a significant association, though results were consistently positive. In addition, many of the measured impacts are of uncertain clinical significance, as noted in the Morello-Frosch paper. Taken collectively, we find this evidence continues to be strongly suggestive of a causal relationship but does not sufficiently support inclusion of this endpoint in the 2016 Socioeconomic Analysis.

The new studies finding associations between PM and autism may warrant additional research, but we do not recommend including this endpoint at this time, due to the 1) acknowledged lack of understanding of a possible biological mechanism, 2) the lack of concordance between results based on spatial differences in exposure and those based on exposure during and following gestation in the Raz et al. study, and 3) the small sample size of the Volk et al. study.

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